Interdepartmental Conference

FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, SCHOOL OF MEDICINE

Influenza 1968—A2/Hong Kong/68

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DR. ST. GEME:* We wish to present the tragic confrontation between a pregnant young woman and A2/HONG KONG/68 and in so doing correlate the clinical, radiographic, pathologic and virologic aspects of this epidemic viral infection. Later, we will plumb the tale more deeply and unfold our knowledge about the influenza virion and the various facets of resistance which are important to the host in this confrontation.

As a brief prologue while setting the stage for the presentation of the case, I would like to review the "Recommendations for Influenza Immunization and Control in the Civilian Population —1965-66" which was published in July of 1965 in the Morbidity and Mortality Weekly Report (MMWR) of the National Communicable Disease Center. The high risk groups for influenza immunization included persons with chronic debilitating diseases of cardiovascular, bronchopulmonary, and metabolic nature, the elderly, and pregnant women. "It is to be noted that some mortality was observed among pregnant women during the 1957-1958 influenza A2 epidemic both in this country and abroad. It has not, however, been demonstrated in subsequent years."

The following recommendation was published in the MMWR of July 16, 1966: "Some increased mortality was observed among pregnant women during the 1957-58 influenza A2 epidemic . . . Similar data are not available for subsequent years and, therefore, routine influenza immunization during pregnancy is not recommended unless the individual also falls into one of the above noted high-risk categories."

In July of 1967 the Recommendation of the Public Health Service Advisory Committee on Immunization Practices was essentially the same. The MMWR of June 29, 1968, contained the recommendation that "routine vaccination of healthy groups of adults and children is not recommended. This recommendation is particularly relevant in 1968-69 because epidemic influenza is not expected to occur." Now these are the recommendations of mere mortals.

In the MMWR of August 31, 1968 there was a statement that in the preceeding July influenza virus, A2/HONG KONG/1968, was isolated on the China mainland in the area of Hong Kong. The strains of virus isolated from this large outbreak

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showed a decided antigenic shift from previous strains. Similar viruses were subsequently isolated from an outbreak in Singapore. Significant concern developed that the United States was going to be confronted, some ten to eleven years following the 1957 epidemic of influenza (A2/JAPAN/305), with another large-scale epidemic.

The MMWR of August 31, 1968 contained the recommendation that the "currently available bivalent and polyvalent vaccine be given only to persons at highest risk of mortality or severe complications as a result of influenza." With the eventual availability of specific monovalent vaccine it was suggested that the chronically ill and the older age groups should be vaccinated or revaccinated with it. There was no comment about the pregnant woman.

We have asked Dr. Glenn Bradley of the Department of Obstetrics and Gynecology to present the clinical protocol concerning the previously mentioned unfortunate young woman.

Fatal Influenza in Pregnancy

DR. BRADLEY:* The patient was a 27-year-old, married, Caucasion woman, Gravida 4, Para 1, AB2, whose last menstrual period was July 20, 1968, and whose estimated date of confinement was April 27, 1969. She was admitted to Harbor General Hospital on December 27, 1968. She had received irregular prenatal care but her prenatal course was uncomplicated until five days before admission, when she noted the onset of chills, fever, productive cough, and shortness of breath as well as myalgia and headaches. Two days before admission she experienced increasing cough with mucoid sputum. On December 26, because of increased shortness of breath, she was put into hospital elsewhere with a diagnosis of pneumonia and treated with tetracycline. An x-ray film of the chest was suggestive of possible tuberculosis and she was referred to Harbor General Hospital.

She had rheumatic fever at age 10, requiring bed restriction for several months. She was allergic to penicillin and lincocin. There was no familial history of tuberculosis. Her father had died of carcinoma of the lung.

When examined, the patient was observed to be thin. She was sitting up in bed in moderate respiratory distress with obvious tachypnea. Blood pressure was 116/70 mm of mercury, pulse 120, respirations 50 per minute and shallow, and temperature 38.3°C (101°F). Respirations were symmetrical and the diaphragms moved easily. Generalized bronchial breath sounds were detected, with diffuse rhonchi and moist rales. The heart had a regular rhythm and the third heart sound was audible. There was a questionable opening snap, but no murmurs were heard. The abdomen was soft and the fundus was palpable two fingerbreadths above the umbilicus. There were irregular moderate-quality uterine contractions every five to seven minutes. The estimated fetal weight was only one pound. Fetal heart tones were regular, 120 per minute. The cervix was 90 percent effaced, the os closed, and the vertex was at —2 station. There was suggestive slight cyanosis of the nailbeds, and the skin and mucus membranes were mildly cyanotic. The impression on admission was influenzal pneumonia complicated by secondary bacterial infection.

Admission laboratory data included a leukocyte count of 13,700 and hematocrit of 28 percent. Two days later leukocytes numbered 15,800 with 56 percent bands, 39 percent polymorphonuclear cells and 5 percent lymphocytes. Plasma electrolytes were unremarkable and blood gas analysis revealed a pH of 7.39, pO_2 of 66, pCO_2 of 32, and an oxygen saturation of 93 percent. A Gram stain of the sputum revealed many white cells and a moderate number of Gram-positive diplococci. Urinalysis was within normal limits. An x-ray film demonstrated massive infiltration and consolidation of both lung fields with obscuration of the cardiac shadow. (This and subsequent films will be discussed later.)

The patient was given cephalothin, nasal oxygen, and intermittent positive pressure assisted ventilation. The patient's temperature remained at 38.3°C, occasionally spiking to 39.4 (103°F). The blood gases remained unchanged. Because of the low hematocrit, 2 units of packed erythrocytes were administered. A consultant suggested that the patient would benefit from a pulmonary lavage, which was performed under general anesthesia. At the time of the lavage the patient had cardiac arrest for approximately 5 minutes but responded to conservative measures of resuscitation. A tracheostomy and bronchoscopy were performed, and specimens submitted at that time yielded viridans streptococci, the same organism

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that was cultivated from the sputum on admission (virologic studies will be discussed below. See also Table 3).

The patient was placed on a volume respirator. Following the pulmonary lavage there was some improvement in pulmonary findings. Cephalothin was continued and digoxin and cortisone were added. Blood gases were determined serially. The profound acidosis (pH 7.01) following cardiac arrest was corrected progressively by the administration of bicarbonate and calcium gluconate. Chest films following pulmonary lavage revealed little change. Fifteen hours later minimal clearing of the infiltrate was noted. The patient was placed on the volume respirator again and an anectine drip was required to keep her from resisting the apparatus. On the fourth hospital day sinus tachycardia and supraventricular tachycardia occurred. Soon thereafter severe subcutaneous emphysema involving the upper torso, the neck and face was observed. An intratracheal tube was inserted at the tracheostomy site. A second cardiac arrest occurred, and resuscitation restored spontaneous cardiac activity. Films of the chest at that time showed severe pneumomediastinum, but no pneumothorax. During an attempt to place a cuffed endotracheal tube, cardiac arrest occurred again but this time resuscitation was unsuccessful. The patient was pronounced dead five days after admission to the hospital.

DR. ST. GEME: So that we may develop an expanded view of our recent experience with epidemic influenza, our colleagues will discuss the radiographic, pathologic, and virologic aspects of several cases in addition to that of the young woman described above.

Radiographic Features

DR. TORRANCE*: It would be difficult, looking at the admission chest film (Figure 1) in the case of this young woman, to diagnose viral pneumonia or influenza pneumonia. One would place other entities higher in the differential diagnosis. The picture is that of an overwhelming exudative process in the pulmonary alveolar spaces. One could not comment on the presence or absence of interstitial involvement. There is no direct evidence of it. Our initial diagnostic consideration would be one of overwhelming pulmonary edema. We have seen films resembling this one in heroin addicts, following the injection of the drug with whatever is used to "cut" it. We have seen the same radiographic pattern in overwhelming intoxications, with extensive aspiration, with sudden acute overwhelming left ventricular failure, and with acute hypersensitivity reactions as in transfusion reaction. All these diagnoses must be allotted their place and rank in the evaluation of each film.

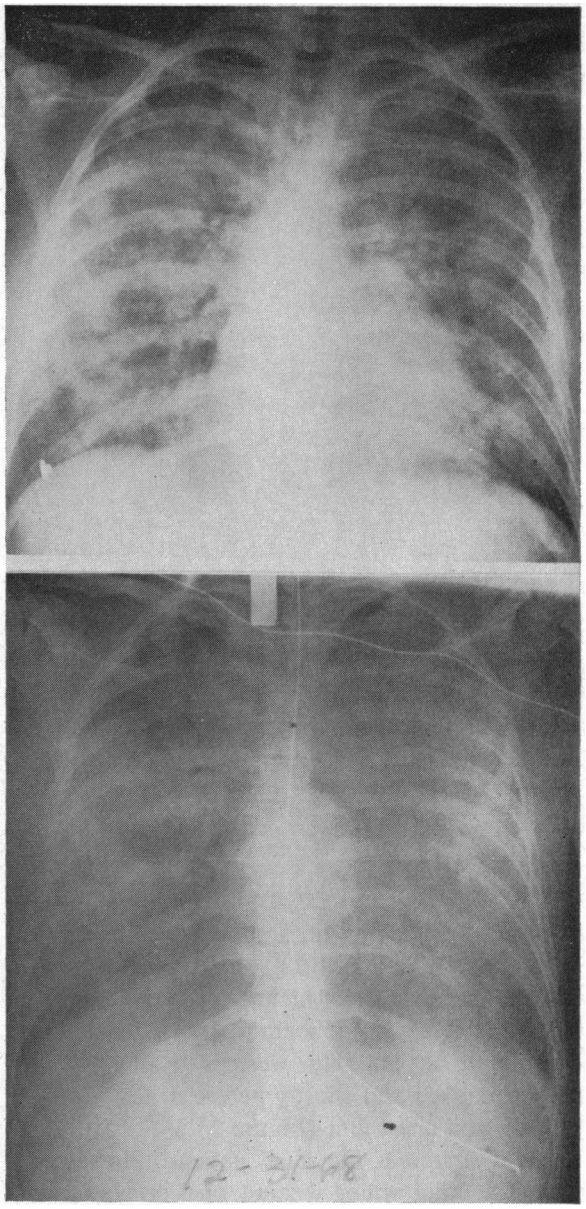

Figure 1.—X-ray films of chest in propositus case. *Above*, diffuse influenza virus pneumonitis on the day of admission. *Below*, extensive change throughout both lung fields shortly before death.

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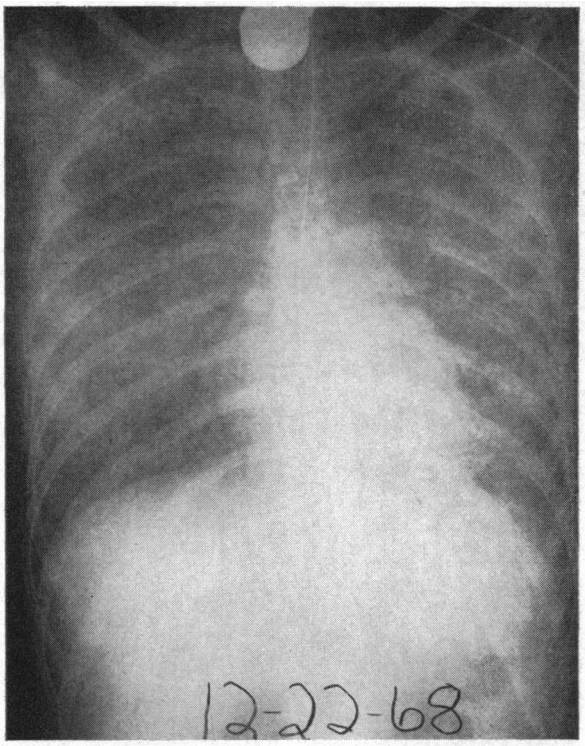

Figure 2. — The patient in this case was a 33-year-old pregnant woman with diffuse influenza virus pneumonitis. This film was obtained after pulmonary lavage, shortly before death.

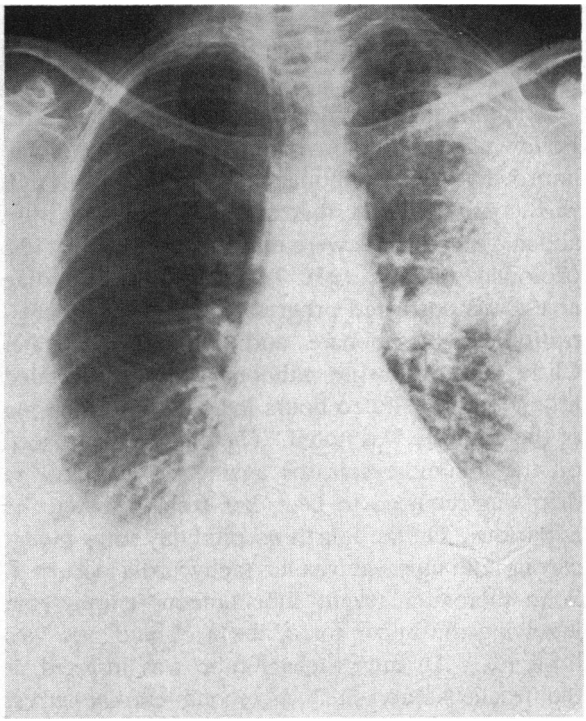

Figure 3. — X-ray film of chest of 66-year-old woman with chills, fever, and cough three days before admission to hospital with staphylococcal bacteremia (Case 1, Table 2). Death ensued within 12 hours of admission and influenza virus was isolated from lung tissue at necropsy.

We see next rapid extension of the infiltrate to involve all segments of both lungs diffusely and symmetrically (Figure 1). In this film we can assay how extensive it has become from the well-defined air bronchogram, indicating massive consolidation. This film was taken after the pulmonary lavage and shortly before death.

This next chest film (Figure 2) looks as though it might represent the same patient. However, it was of another young woman, also pregnant, who was admitted with a similar history and subsequent rapid deterioration and death.

It is important to emphasize that the films of these two different patients were taken after pulmonary lavage, and one wonders what role this attempted flushing of the lungs played in the development of these radiographic patterns.

The last film (Figure 3) obtained from an elderly woman with virologically documented influenza, shows still another pattern—that of focal lobular pneumonia, which may be associated with some tissue breakdown. There is coarse "honeycombing" or excavation, a finding that might suggest staphylococcal pneumonia rather than influenza. This patient died shortly after admission to hospital with staphylococcal bacteremia, and influenza virus was isolated from the lung at necropsy.

When we review the literature for descriptive treatment of the radiographic changes in these viral pneumonias, we can approximate accurate summary by saying that "anything is possible." The lesion can mimic any other infection, focal or diffuse, or even pulmonary edema.

Pathology

DR. HIROSE:* In December of 1968 we encountered for the first time in our autopsy suite a relatively unusual situation, a very severe tracheobronchitis with pronounced hyperemia of the trachea and associated areas of purulent exudate. This was puzzling but we were aware that influenza virus was present in our patient population. The most striking finding at necropsy was the voluminous lungs observed in six patients that we believed had influenza. In four of the six cases the influenza virus was isolated. In the other two the morphological features were so characteristic that we felt confident that the diagnosis was influenza.

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The gross autopsy diagnosis of influenza is suggested by tracheobronchitis, with pronounced hyperemia of the upper respiratory tract, and enormous distended extremely heavy lungs.[1] The lightest lungs of our series weighed 1,650 grams, which is at least twice the combined weight of normal lungs, and the range was up to 4,000 grams.

Consistent with the remarkable tracheobronchitis seen grossly, microscopically there is desquamation of the respiratory epithelium with exposure of a necrotic and edematous lamina propria (Figure 4). In spite of extensive necrosis of the lamina propria region, there is scant inflammatory reaction in the subjacent tissues. Focally, ducts leading to the mucous and mucoserous glands are lined by squamoid regenerative epithelial cells. The grossly seen hyperemia is due to pronounced dilation and congestion of the subepithelial vessels and diffuse hemorrhage throughout the stroma.

The purulent and necrotizing process extends down into the bronchi and the bronchioles, where there is also desquamated and regenerative epithelium. In the alveolar region proliferation of alveolar epithelial cells is evident. One may also see the classical histological feature of the pulmonary parenchyma in influenza, hyaline membranes (Figure 4). Hyaline membranes are characteristic of influenzal pneumonitis, yet based on this observation alone one cannot state that the morbid process is influenza. Hyaline membranes may also be seen in radiation, uremic and rheumatic pneumonitis, or in oxygen toxicity in its early stages.

With the passage of time thrombi are found in capillaries of the alveolar wall, and extravasation of blood can be seen within the alveolar lumina.

In addition to hyaline membranes, there are thickened alveolar septae. One could suggest that interstitial pneumonitis and diffuse edema cause the excessive weight of the lungs.

Superimposed infection may lead to areas of bronchopneumonia. So the lungs of influenza at necropsy are at times clouded by the presence of other types of infectious processes, and in the past pneumococci, streptococci and staphylococci have been implicated in the pathogenesis of fatal influenza.

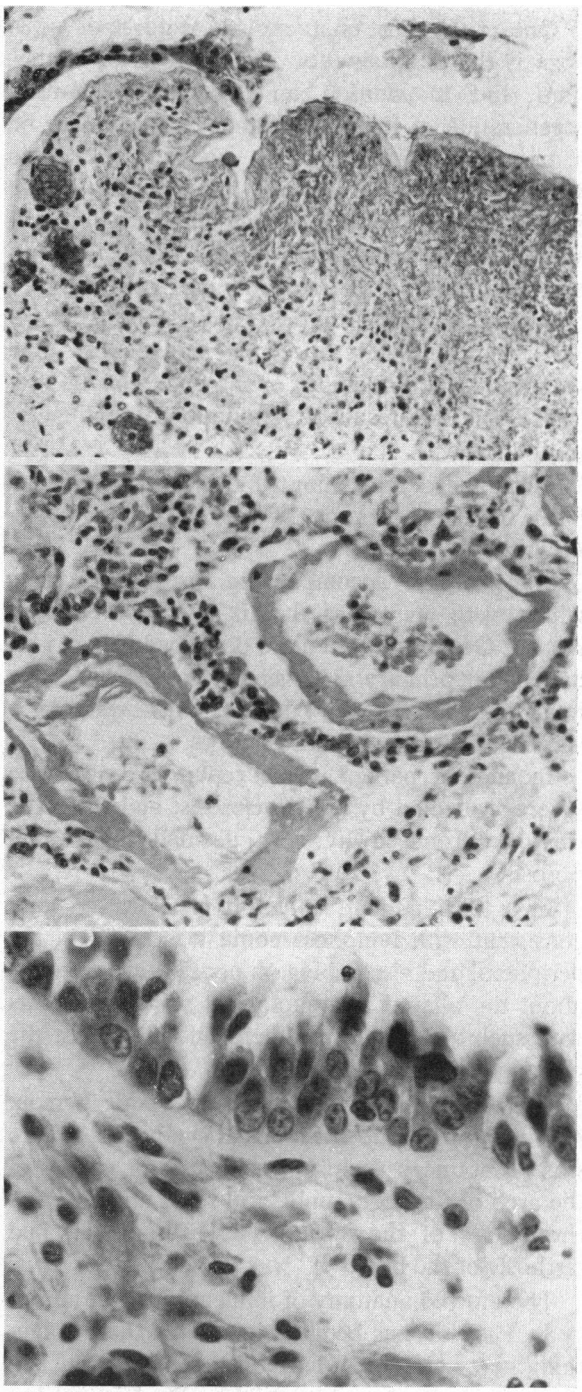

Figure 4.—Photomicrographs in propositus case. *Above*, acute tracheitis with loss of epithelium, necrosis and edema of the lamina propria. (Hematoxylin and eosin stain. Medium power.) *Center*, hyaline membranes lining alveoli of lungs. (H. & E., medium power.) *Below*, the mucous membrane of a bronchus with prominence of the basement membrane. (H. & E., high power.)

One of the most characteristic features of influenza is the desquamation and necrosis of epithelium, and, in addition, an adjacent concomitant regeneration of the epithelium. This seems to be a unique feature. At high power microscopic visualization, variability of the nuclei of the bronchus and bronchiolar epithelial cells is well shown. If there happened to be available a Papanicolaou-stained sputum containing epithelium of this type it would alarm the cytologists. The atypical cells would be suspect for malignancy. One wonders if the variability of the nuclei of the epithelial cells is a result of stimulation of epithelium by the virus.

Pronounced thickening of the basement membrane is also a feature of the lung in influenza (Figure 4).[2]

Some of the accompanying disease processes which were present in the six necropsy cases at Harbor General Hospital are described below. Our patient for primary discussion was pregnant. The fetal lung did not show hyaline membranes, nor was the virus recovered by culture.

In another patient, the coronary arteries were severely affected by arteriosclerosis, and the heart was compromised by very decided myocardial fibrosis.

In a third patient, a lymphoproliferative state consistent with lymphosarcoma was noted in the peripheral and visceral lymph nodes. One wonders about the altered immunological state in patients with such a disorder and their ability to resist the onslaught of influenza virus.

The fourth patient, a relatively young person, 44 years, had a subclavian steal syndrome. There was pronounced occlusion of the major vessels of the arch of the aorta, unilateral renal atrophy, and thrombosis of the aorta. The fifth patient had cirrhosis of the liver.

The morbid anatomy of influenza seen at autopsy in 1968-69 has been reviewed. Is there something new being recorded? In a relatively ancient monograph, published in 1920 by Dr. Winternitz,[3] there is shown the classic feature of influenza, namely, tracheobronchitis with pseudomembraneous exudate and profound hyperemia of the tracheobronchial tree.

The lungs are pictured as being voluminous and distended, with firm, edematous, hyperemic parenchyma and occasional bronchopneumonia. Scattered foci of alveolar hemorrhages can be found. On cut sections, gray infiltrates are reminiscent of an interstitial fibrosis or fibrin deposition. The extremely heavy lung, the voluminous lung, the edematous wet lung, and the lobar involvement are emphasized. Influenza is called a "panlobar" pneumonia.

Depicted histologically is the tracheobronchitis manifested by necrotic epithelium, a hyperemic lamina propria, and the relative paucity of the acute inflammatory exudate in the lamina propria. Classic hyaline membranes and extravasation of blood into the alveoli may be seen. The gross diffuse grayness of the parenchyma is identified microscopically as diffuse fibrin deposition.

So, the morphology of influenza 1968-69 has been duplicated or revisited and in essence is similar to that which was described in 1920 by Dr. Winternitz.

Laboratory Procedures

DR. IMAGAWA*: As in most other viral infections, the laboratory procedures for influenza diagnosis would include isolation of the etiological virus or the demonstration of specific antibody rise in the patient's serum. During the recent epidemic we relied primarily on the isolation of the influenza virus with subsequent typing and identification of the isolates. Virus isolation would be an important procedure for identifying the agent responsible for an epidemic. Once the prevailing virus is isolated and typed, diagnosis of other cases can be carried out by serological methods.

The laboratory host of choice for the isolation of influenza virus is still the chick embryo. Fertile eggs incubated for 10 to 14 days are inoculated into the amniotic sac. After two to four days of incubation a specimen of the amniotic fluid is tested for hemagglutinating activity.

Isolation of influenza virus has been accomplished also by inoculation of primary monkey kidney cell cultures. Generally on primary isolation, the virus does not cause clear-cut cytopathic effects, and the presence of the virus must be detected by an indirect method. Since influenza virus possesses hemagglutinins, a technique described as hemadsorption can be used. This is a procedure in which the hemagglutinins on the infected cell surface cause the red blood cells to adhere in clumps to the host cell monolayer.

We employed both the chick embryo and the

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TABLE 1.—A2/HONG KONG/68 *Isolates from Seven Ambulatory Patients*

Age	*Diagnosis*	*Specimen*	*Onset of Illness*	*Specimen Taken*
Adult	Influenza	Throat swab	12/ 3/68	12/ 3/68
Adult	Pneumonia	Sputum	12/ 4/68	12/ 9/68
Child	Vomiting and diarrhea	Throat swab	12/ 7/68	12/ 8/68
Child	Influenza	Throat swab	12/15/68	12/17/68
Child	Influenza	Throat swab	12/14/68	12/15/68
Child	Influenza	Throat swab	12/14/68	12/14/68
Child	Influenza	Throat swab	12/16/68	12/17/68

TABLE 2.—A2/HONG KONG/68 *Isolates from Postmortem Materials*

Patient	*Sex*	*Age*	*Specimen*	*Virus Isolation*
1	F	66	Bronchus	Cell culture +
				Egg +
2	F	60	Lung	Cell culture +
				Egg +
3	M	44	Lung	Cell culture +
				Egg +
4	F	27	Lung	Cell culture —
				Egg +

cell culture procedures for isolation of influenza virus. The freshly isolated viruses were identified as strains of A2/HONG KONG/68 by the hemagglutination-inhibition and the hemadsorption-inhibition tests.

The isolation of A2/HONG KONG/68 virus strains from seven ambulatory patients is summarized in Table 1. These isolates were made in monkey kidney cell cultures. Successful isolation of the viruses can be credited to the very short interval between the onset of the disease and the obtaining of clinical materials for inoculation. Specimens for viral isolation attempts were obtained as early as possible in the course of illness.

Table 2 summarizes the isolation of the epidemic strain of influenza virus from postmortem materials. Both the monkey kidney cell culture and the chick embryo procedures were used. Virus isolation was accomplished from the bronchus or from the lungs. Both isolation techniques yielded the virus, with the exception of the lung from the case under discussion (Case 4, Table 2) which yielded no virus with the cell culture method but was positive by the chick embryo procedure.

Table 3 summarizes the virus isolations in the case presented in this conference. On December 12, 1968, before the patient died, the lung lavage and the sputum inoculated into monkey cell culture yielded influenza virus A2/HONG KONG/68. The postmortem material from the lung inoculated into cell culture was negative, but the chick embryo system yielded virus. The tracheal epithelial material inoculated into cell culture was again negative, whereas the chick embryo was positive. It would appear from these studies that there is a higher rate of isolation in eggs than in cell cultures. However, it is the opinion of most investigators that the rate of isolation is essentially similar in eggs and in cell cultures. Virus was not recovered from the placenta and the heart; likewise, the heart and the lung from the fetus yielded no virus.

TABLE 3.—A2/HONG KONG/68 *Virus Isolation from Case Discussed in Present Interdepartmental Conference*

Date	*Specimen*	*Virus Isolation*
12/30/68	Lung Lavage	Cell culture +
	Sputum	Cell culture +
1/ 2/69	Lung	Cell culture —
		Egg +
	Tracheal Epithelium	Cell culture —
		Egg +
	Heart	Cell culture —
	Placenta	Cell culture —
1/ 2/69	Fetal lung	Cell culture —
		Egg —
	Fetal heart	Cell culture —
		Egg —

Finally, I would like to discuss briefly the relationship between Hong Kong 1968 strains and the earlier A2 strains. It was recently reported that antisera produced against Hong Kong 1968 strains clearly demonstrated an antigenic relationship with the earlier A2 viruses.[4] However, the Hong Kong influenza viruses represented a major antigenic drift and the identification of the Hong Kong strains may not be possible with specific antisera produced against the earlier A2 reference strains. Nevertheless, these new isolates are still classified as A2 influenza viruses.

DR. ST. GEME: The provocative clinical and laboratory facets of the 1968 epidemic, as we witnessed it in our own medical center, raise the most fundamental questions of the innate resistance of the human host and the complexity of the genetic, antigenic and biochemical attributes of the influenza virus. The following sections of this conference represent an attempt to acquire some perspective of these questions.

Host-Virus Relationship And Lower Respiratory Tract

DR. ZIMENT*: First of all I think we should clarify that the virus we are talking about did not really originate in Hong Kong in July 1968; the evidence

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is that it originated in China and that it was probably a fairly close relative of its notorious predecessor of 1957. It used Hong Kong as an embarcation point for a world cruise and it landed in Los Angeles roughly five months later. Its subsequent depredations resulted in this symposium.

Infection of a host by the influenza virus can occur when the agent encounters the susceptible respiratory mucosa. The cilia of the epithelium present receptor areas to which the influenza virus becomes very firmly attached, causing inhibition of ciliary activity. The goblet cells are also affected, and lose their ability to produce mucus, which in turn may increase the mucosal susceptibility to further invasion.

Following the invasion of the respiratory mucosa there may be a lag phase: thus, members of a family may derive their initial infections at different periods yet symptoms may develop in all of them simultaneously. This is probably related to the fact that external factors initiate the breakdown in the host-virus relations, and perhaps chilling or a change in weather are important determinants in the development of symptoms. Viral pathogenicity probably depends upon the release of toxic products, some of which are purely speculative. It is well known that the virus inhibits the chemotactic response of the leukocytes, and it also appears to inhibit the ability of the granulocytes to engulf bacteria.

The virus inhibits the cilia of the epithelium and, subsequent to that, causes death of the cells; it appears that the goblet cells are also killed. If the virus invades the lower reaches of the respiratory tract, it similarly destroys the various types of cells lining the bronchioles and alveoli. In particular, the pneumocytes known as Type I cells, and the macrophages known as Type II cells are damaged and lose contact with the basement membrane, thus contributing to the formation of a hyaline membrane. A true alveolar capillary block seems to be produced, and it is also possible that surfactant is damaged, leading to micro-atelectasis. As a result of all these changes the alveoli are severely damaged and pronounced hypoxia may result.

It is well known that pregnant women are particularly liable to the ill effects of influenza pneumonia.[5,6] This is well illustrated in the patient who is presented in this conference. She was five and a half months pregnant, and at that time in pregnancy the patient suffers several disadvantages of hemodynamic and pulmonary function. The diaphragm is elevated and there may be associated atelectasis in the basal parts of the lung; there is an increased hemodynamic load, and an increased oxygen requirement imposed by the fetus and placenta. The heart is less able to make a full compensatory adjustment to the stress of infection, and the addition of severe pneumonic involvement exacerbates the tendency toward hypoxia. The presence of heart disease will obviously embarrass the situation further, and many of the deaths in epidemics have been associated with the presence of mitral stenosis and pulmonary hypertension. It is not clear whether the pregnant woman is also at a disadvantage from other than these purely mechanical factors. Thus, it is possible that there is impaired production of the various antiviral factors or of surfactant.

The toxic effects of the virus infection may result from release into the bloodstream of antigenic material both from the virus and from the damaged tissues. The patient has a generalized illness and in some cases there may even be an allergic reaction to viral products, but the dangers of the disease are associated with the embarrassment to the respiratory process and the resulting hypoxia. Secondary bacterial infection of the lung is an important complication, and staphylococcus aureus, for unknown reasons, is particularly likely to complicate influenzal pneumonia.[5] The virus certainly prepares the way for bacterial infection by disruption of the respiratory mucosa and by damage to the underlying blood vessels, as well as by inhibiting phagocytosis.

This review of the host factor is based on accepted and well understood phenomena, but to move on to how the host reacts against the virus is to tread on ground which is not so steady at all. However, it appears that the immunologic response to influenzal respiratory infection will be incomplete, since the bloodstream is not invaded in the usual case. Defense against the virus depends in part upon the production by the host of immunoglobulins. The specific immunoglobulin that is most important to the respiratory tract is IgA, and this is secreted by the mucosa. It also is formed in the bloodstream, and the amount in the mucosa is perhaps only one-tenth the amount in the blood. But it is of considerable interest that persons with agammaglobulinemia are able to react quite normally to viral infections, so obviously immunoglobulins do not play a major role. It is evident that lymphocytic factors also are involved, for in pa-

tients with impaired delayed hypersensitivity severe generalized disease may occur in virus infections.

It has been clearly established in the last few years that viral infections of almost any type stimulate the host to produce a curious protein called interferon.[7] Time does not permit discussion of the very complex nature of the mechanism involved in the production and action of interferon, but its production is primarily a result of viral infection of the cells, although it is quite possible that many other factors which occur both normally and abnormally influence the mechanism.

The survival of the virus is facilitated by the production of several postulated rather than absolutely confirmed factors, and these rejoice under rather curious names, such as stimulon, enhancer, and blocker, which in one way or another interfere with the action of interferon.[7] Similarly, viral enzymes such as neuraminidase facilitate viral pathogenicity. On the other hand, the host is able to respond to the viral infection by producing a number of equally ill-understood non-specific inhibitors: in particular the literature refers to alpha, beta and gamma inhibitors, which are either mucoproteins or lipids or other complex proteins.[8]

The host probably does offer resistance in various other ways about which we can only speculate. Thus influenza is more likely to occur in persons who are of blood group O, although there is no further explanation as to why this should be.

Regarding the therapy of our ill-fated patient, I wish to state that we felt pulmonary lavage was justified since we were dealing with an alveolar filling defect, with some similarities to alveolar proteinosis which responds well to lavage.[9] The role of specific drugs is not yet established, and the only drug which has been commercially available for use in influenzal infections is amantadine hydrochloride, which interferes with the ability of the virus to penetrate the cell. This has been found to be of specific value in the prevention of A2 influenza infection, but its use was not recommended by the Public Health Service. We were left with as primitive a way of dealing with this epidemic as we had in 1957.

Genetic Aspects of Antigenic Drifts of Influenza Virus

DR. BALUDA:* Although not until the 1930s was it established that a virus was the causative factor in influenza, the disease is not a new malady of the human population.[10] There are descriptions of influenza infections in humans and in animals which date from the 12th century, and 31 pandemics have been recorded since the 16th century. Three major pandemics have occurred within the past 50 years; the last one, referred to as the "Hong Kong Flu," appeared in 1968. During these pandemics, almost the entire population is exposed and develops antibodies against the virus. Every time there is a major epidemic, it is caused by a new virus. This periodic appearance—approximately every 10 years—of a new virus capable of infecting a previously immune population is a unique feature of influenza viruses and is due to a phenomenon called "antigenic drift." The new virus contains a different, or modified, antigen on its outer surface and is not neutralized by antibody made against the old viruses. This means that not only can the new virus infect a population exposed to the old viruses, but prophylactic vaccination with known strains is either ineffective or only moderately effective. Stable variants, or strains, differing in antigenic properties are known to exist among all viruses, but the regular appearance of new influenza viruses had been a puzzle to virologists and epidemiologists. Only recently has it been possible to understand this unique nature of influenza virus, albeit without knowing how to cope with it.

Before attempting an explanation for the basis of this antigenic drift, let us first examine the structure of the influenza virion and its mode of replication.

Structure of Influenza Viruses

Influenza viruses contain about 0.8 percent RNA, 74 percent protein, 18.5 percent lipids and 5 to 7 percent non-nucleic acid carbohydrates.[10] In the electron microscope, influenza virions appear pleomorphic ranging from spherical to filamentous forms with a diameter of 800-1,100A (angstrom units).[11] The inner core of the virus, or ribonucleoprotein (RNP), consists of the RNA genome complexed with protein and is a rather flexible rod-shaped structure with subunits which appear to be in a helical arrangement.[12] The RNP core is enclosed in a lipoprotein envelope which has cylindrical spikes on its outer surface. These spikes, 90A long and 15-20A in diameter, appear to consist mostly of hemagglutinin, the protein which agglutinates erythrocytes. Between the spikes

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there is another protein, neuraminidase; this enzyme digests mucoproteins and facilitates the release of virus during its maturation from the cell surface. The viral envelope contains lipids which are mostly of cellular origin and some host cell antigen—for example, blood group antigen.

Antigenic Structure

Three major antigens are used in classifying influenza viruses[13]:

1. One is the internal antigen, also called RNP antigen, which determines whether the virus is type A, B or C. This antigen is detected by complement fixation and is referred to as the CF (complement fixing) antigen. The ribonucleoprotein is a stable component of the virus as determined by its antigenicity—that is, it is the same for all members of the type A group regardless of whether they infect man, swine, horse, duck or chicken. Minor variations in primary amino acid sequence, not detectable by complement fixation, cannot, however, be ruled out. The RNP antigen is a peptide with a molecular weight of 50-70 x 10^3 daltons.

2. The hemagglutin antigen (HA) on the spikes, also referred to as the "V" antigen, is detected by virus neutralization, or hemagglutinin inhibition, and is strain-specific—that is, it is different for strains A0, A1, A2, and others. This is the antigen which elicits the formation of protecting antibody. A new virus, capable of causing an epidemic, must possess a hemagglutinin which is sufficiently different so that it is not neutralized by antibodies made against that of the existing strains. HA subunits obtained by disrupting the virus with detergent—e.g., deoxycholate—consist of glycoprotein rods, 140A long x 40A wide with a molecular weight of 47 to 75 x 10^3 daltons. The individual rods are monovalent—that is, can block red cell agglutination but are incapable of causing red cell agglutination. In the absence of detergent, they clump and appear as rosettes in the electron microscope; the rosettes can cause agglutination of red blood cells. The host antigen, which is present in the envelope, is a carbohydrate and is covalently linked to the hemagglutinin subunits.

3. The other major virus antigen which is present in the envelope is the neuraminidase (NA). This enzyme differs serologically and chemically from HA and can vary independently of HA. Antibodies against this enzyme do not appear to play a major role in protection against virus infection, although the antineuraminidase antibody may limit subsequent infection by preventing the release of virus from infected cells. Purified neuraminidase units are oblong structures about 85A long and 50A wide with a centrally attached fiber 100A long and a diffuse tail, or a small knob, of 40A in diameter. These particles consist of peptides with a molecular weight of 50 x 10^3 daltons which are probably linked to the HA unit through the carbohydrate moiety in the virion.

Other proteins which make up less than 10 percent of total virion protein and appear as peptides of molecular weight less than 20 x 10^3 daltons in gel electrophoresis have not been characterized.

Viral Genome

The genome of influenza viruses consists of single stranded ribonucleic acid (RNA). It has some unique features which hold the clue to the antigenic drift. Unlike the genome of other single stranded RNA viruses, the influenza virus RNA is heterogeneous and consists of 4 to 5 molecules of varying sizes ranging from 7 x 10^5 daltons to 2 x 10^5 daltons in molecular weight.[14,15] Five distinct species of viral RNA have been separated by gel electrophoresis.[16,17] From the profile of the viral RNA in sucrose gradients and in gel electrophoresis, it appears that these RNA molecules are present in a 1:1 ratio in fully infectious (complete) virus. In incomplete (von Magnus effect) virus the larger species are either absent or present in only 2 percent of the virions.[18,19]

Virus Replication

The replication of influenza virus can be divided into three major phases: (1) replication of the RNA genome, (2) synthesis of viral proteins, and (3) maturation and release of virions at the cell surface.

1. As with other RNA viruses, the replication of influenza RNA depends upon a virus specific enzyme, RNA-dependent RNA polymerase. Complimentary RNA, or minus strand, is made using the incoming viral RNA as the template, and in turn it is used to make new plus (viral) RNA strands.[20] The synthesis of new viral RNA takes place via an RNA replicative intermediate (RI) which consists of one minus strand to which are attached several nascent plus strands.[21]

2. Viral RNA acts as messenger RNA for making virus-specific protein, for example HA, NA, internal

protein and RNA dependent polymerase. Recently polysomes involved in the synthesis of peptides were isolated from infected cells and were found to contain both plus and minus RNA strands.[22] The location of different genes in the different strands of viral RNA is unknown.

3. Maturation involves packaging different RNA species in the form of ribonucleoproteins into an envelope which is made at the cell membrane but contains mostly viral antigens. There should also be a mechanism for excluding minus strands which are not found in virions. Nothing is known about the processes involved. Maturation is completed as the virion buds off the cell surface.

Mechanism of Antigenic Drift

According to the current dogma of molecular biology, the antigenicity of the viral coat protein is determined by its amino acid sequence, which in turn is coded by the sequence of nucleotides in the viral genome. Any major antigenic shift is therefore the phenotypic expression of a different viral genome. The evolution of a genetic variant can take place either by mutation, genetic recombination or strand exchange.

Mutation: Due to spontaneous mutations or to errors in copying the nucleic acid, there may be occasional alterations in the base sequence of the RNA which in turn causes changes in the amino acid sequence and in the antigenicity of the protein. A mutation in the hemagglutinin gene could give rise to a new variant. Most of the stable variants of RNA viruses arise by mutation and selection.

Mutations have also been shown to cause variations among influenza viruses. In the laboratory, such mutant strains can be obtained in various ways; for example, mutants involving changes in the virus coat protein can be obtained by growing the virus in the presence of antiserum of low avidity.[23]

Minor outbreaks of influenza between the major pandemics are often caused by minor changes in virus coat protein which arise by mutation and selection. However, mutation alone cannot explain the high frequency of appearance of a new influenza virus strain every eight to ten years, since similar changes do not take place among other single stranded RNA viruses—such as mumps, rubella, measles, polio, NDV and arboviruses—which infect man and animals. It is well established that these viruses can also develop variants or mutant strains, but the mutant viruses are stable and, unlike influenza viruses, can be isolated in recurring epidemics.

Genetic Recombination: The second possibility of forming a new virus is by recombination, which involves the exchange of covalently linked parts of the genome between two or more viruses growing in the same host. Thus the progeny virus will have new genetic material which is a hybrid of the two parent viruses. Recombination occurs regularly among DNA viruses. This process of exchange takes place by excision and ligation of double stranded DNA. The relatively stable secondary structure of DNA is almost an absolute requirement for such an exchange. It is not known whether such a mechanism of recombination between RNA viruses exists. Using DNA virus as a model, one would expect that recombination can only take place between two double stranded RNA molecules or between replicative intermediates which are partially double stranded. However, since there is preferential replication of plus (viral) RNA strand, there are relatively few RI's compared with the number of plus strands formed,[21] and the chances of recombination between the RI's of RNA viruses is much less than that between the DNA's of DNA viruses. Indeed, recombination is a rare event among RNA viruses. With Newcastle disease virus, heterozygotes and phenotypically mixed virions can easily be obtained by infecting a host with two different strains,[24] but recombination has not been demonstrated conclusively. With poliovirus, at the most 0.4 percent of the progeny viruses might be hybrids resulting from recombination.[25] On the other hand, hybrid viruses can easily be formed by infecting cells with two different influenza viruses.[26,27] The percentage of hybrid virions in the progeny can be as high as 94 percent of the total virions.[26] So high a frequency of hybrid formation cannot be explained by classical recombination.

Strand Exchange: Strand exchange will be defined as the process that involves exchange of genetic material between two or more viruses growing in the same host but, unlike recombination, it does not involve breakage and reformation of convalent linkages in the genomes involved. This process can take place only in viruses which contain a genome consisting of multiple subgenomic fragments, and thus far it is unique for influenza viruses. In the laboratory, numerous experiments have shown that hybrid virus formation does take place with unusually high frequency if cells are infected with two influenza virus strains.[27,28] The

more related the two infecting virus strains, the higher is the percentage of hybrid virus in the progeny; in chick embryo cells infected with WS and WSN strains, 10 to 94 percent of the progeny may consist of hybrid virions.[26]

Recently, using temperature-sensitive (ts) mutants, it has been found that all ts mutants can be classified into five groups.[28] Exchange of genetic information was possible between the groups, but not within any one group. Exchange of genetic information and formation of hybrid virus have also been shown to take place between animal and human viruses. A classical example of hybrid formation is the X-7 virus obtained by crossing AO NWS (a human strain) with A2-Singapore, 1957 (a strain infecting man, ducks and turkeys).[29] X-7 virus contains the HA of AO, the CF of AO and A2, and the neuraminidase of A2. In gel electrophoresis, it shows three peptides, two of which come from AO and one from A2. Other properties are also hybrid between these two viruses.

There are also natural occurrences of hybrid virus formation. The virus involved in the 1918 human pandemic contained swine antigens,[30] and may, therefore, have been a recombinant between swine and human viruses. Also, some viruses which have been isolated from turkeys and ducks have the same neuraminidase as a human strain.[29]

In human epidemics, constant antigenic drift among influenza viruses has been observed. AO was the predominant virus until 1950, A1 from 1951 to 1957, A2 from 1957 to 1968. The Hong Kong strain (1968) is a strong variant of A2 and might possibly be classified as A3 (Pereira, personal communication), *i.e.*, its hemagglutinin is antigenically different from that of A2 (1957), but contains the neuraminidase of A2 (1957).

Other Changes: In addition to the foregoing genetic changes, there may also be other changes on the surface of the virion which affect its epidemiologic behavior. There are host-induced changes which depend on the type of cell in which the virus multiplies. These changes may be brought about by changes in the membrane structure of the virus.[27,31] This is important because influenza virus appears to infect cells by fusing its outer membrane with the cell surface and releasing its genetic material inside the cell cytoplasm.[32] Thus, any change which would affect cell fusion, such as a change in the lipoprotein of the virus surface, would affect penetration and infection by influenza virus.

Influenza viruses are undergoing constant antigenic drift with the appearance of a new virus every eight to ten years. Such an antigenic variation seems to be unique for influenza viruses and cannot be explained by mutation or true recombination. This unusual behavior of influenza virus is possible because the viral genome consists of multiple subgenomic fragments or RNA molecules. A new hybrid virus can be formed by exchange of one or more RNA molecules when two viruses infect the same host. The large variety of influenza strains which infect different animals and the many minor mutations which constantly change the viral genome provide a large pool of heterogeneous genomes which may contribute to the formation of new hybrid virions. It is, therefore, impossible to predict the nature of future hybrid viruses which can potentially cause new epidemics.

Epidemiology in Los Angeles

DR. ST. GEME: We would be remiss if we failed to place our story about influenza-1968 in its appropriate perspective as one relating the events of only a small portion of an explosive, widespread epidemic.

DR. KAMEI:* The influenza surveillance methods employed to monitor the 1968 epidemic in Los Angeles County depended upon reports on absentees from selected elementary, secondary schools and from available private industries. Information was also studied from hospitals in which patients with upper respiratory illnesses were treated.

Between November 15 and November 20 reports of influenza-like activity were received and investigated by the Los Angeles County Health Department. Throat cultures obtained from these patients revealed the presence of influenza A2 virus, Hong Kong variant.

The first indications of county-wide influenza activity were noted during the week ended December 7, 1968. The peak of the epidemic was noted during the week ended December 28, 1968. By the end of January 1969 all epidemiologic measurements were back to pre-epidemic levels.

Pneumonia-influenza deaths rose sharply during the first week of January. Statistically significant excess "pneumonia-influenza" deaths followed the estimated peak of the epidemic by three weeks.

*Ichiro Kamei, M.D., Chief, Acute Communicable Disease Control Division, County of Los Angeles Health Department.

The estimated excess mortality due to "pneumonia-influenza" during earlier influenza epidemics in the United States, e.g., 1957, 1958, 1960 and 1963, was approximately 12,000, 6,000, 11,000 and 11,000, respectively. During the 1960s, the estimated case-fatality rates nationwide were roughly six or seven per 100,000 population. This rate is essentially the same for the 1968 Hong Kong flu epidemic experience in Los Angeles County.

The maternal mortality rate in Los Angeles County has not changed significantly over the past 15 or 20 years. We do not have information on the maternal deaths associated with the Hong Kong flu. No conclusion can be made regarding the significance of influenza on maternal mortality.

DR. ST. GEME: We will conclude with a brief review of the potential effect of influenza virus infection on the pregnant woman, the encounter which initiated in so devastating a fashion our extensive discussion in this conference.

DR. BRADLEY: With respect to the question of spontaneous abortions occurring in pregnancy complicated by influenza, the available information is indeed sparse. Most investigators are of the opinion that in early pregnancies complicated by influenza there is a higher incidence of spontaneous first trimester abortions. However, this is not a universal view. Whether or not there occurs an increased likelihood of congenital malformation is also debatable. Reports by Saxen[33] in Helsinki, Coffey and Jessop[34] in Northern Ireland, and Hardy[35] in Baltimore would suggest that this is the case.

The overall mortality rate during the 1918 epidemic was approximately 40 percent, as previously mentioned. Harris[36] in 1919 reviewed 1,350 cases of influenza complicating pregnancy occurring in Maryland. In 50 percent of the cases pneumonia developed and 50 percent of these patients died. The statement has been made that this high mortality rate was very likely due to bacterial superinfection in the pre-antibiotic era. It is interesting to note that in Greenberg's[37] review of 216 influenza deaths occurring in New York City in 1957, 10 percent occurred in pregnant females; one-half of the women aged 15 to 45 who died were pregnant. Freeman and Barno[38] in 1959 reported the influenza deaths occurring in Minnesota. In this series also, half of the females aged 15 to 45 who died were pregnant. One may summarize the problem of influenza and pregnancy by saying that during an epidemic the pregnant patient is somewhat more likely to contract this infection, has a greater tendency toward spontaneous abortion and stillbirth, is somewhat more likely to have her fetus affected by congenital malformation, and is in great risk of death should pneumonia develop.

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AUSCULTATION OF VENTILATORY FUNCTION

"Remember in testing dynamic ventilatory function that you can get a great deal of information at the bedside with that archaic instrument, the stethoscope, especially in determining the mechanism of airway obstruction. One can assess the quality and uniformity of air entry and air exchange, the presence or absence of wheezing, its pitch, and the effect upon wheezing and air exchange of having the patient cough or of having him breathe after the spray of a bronchodilator aerosol. Most important (and I urge each of you to incorporate this into your examination of the patient with pulmonary disease), listen to the patient during quiet breathing and then have him do a maximum ventilation maneuver — have him hyperventilate — and watch and listen to what happens to the air entry and to the sounds of air movement and wheezing in his chest. This is the shouldering phenomenon obtained from a simple spirogram. You can get this kind of information by having a patient with chronic obstructive airway disease hyperventilate without any kind of equipment. He will rapidly begin to breathe out and you'll hear a little bit of an air exchange as if he hits an obstruction; you see him turn red, the veins in his neck stand out, and you don't get any air movement. Or in a tight asthmatic, you may begin to hear high-pitched wheezing whereas if you listen to him during quiet breathing, there is no wheezing at all."

—ASHER MARKS, M.D., Miami

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